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McDERMOTT, WILL & EMERY
600 13th Street, N.W.
Washington, DC 20005-3096

EXAMINER
KANTAMNENI, SHOBHA

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SALUH KIVLIGHN,
RICHARD JOHNSON, and MARILDA MAZZALI

Appeal 2009-005057[1]
Application 09/892,505
Technology Center 1600

Decided: January 25, 2010

Before DONALD E. ADAMS, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 16-18. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Oral Hearing held January 7, 2010.

STATEMENT OF THE CASE

Claims 16 and 18 are representative of the claims on appeal, and read as follows:

16. A method of reducing uric acid in a patient in need thereof to treat a condition, said method comprising administering to said patient a therapeutically effective amount of a composition comprising a xanthine oxidase inhibitor, or a pharmaceutically acceptable salt thereof, to achieve a uric acid level in the patient of 4 to 6 mg/dl, wherein said condition is hypertension.

18. A method for treating hypertension in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of allopurinol, or a pharmaceutically acceptable salt thereof.

The Examiner relies on the following evidence:

Baldwin	US 4,032,522	Jun. 28, 1977
Baldwin	US 4,058,614	Nov. 15, 1977
Maeda	US 5,747,495	May 5, 1998
Nakamoto	EP 0 337 350 A2	Oct. 18, 1989

Appellants rely on the following evidence:

Declaration of Bernardo Rodriguez-Iturbe, M.D., submitted October 31, 2007.

Declaration of George Bakris, M.D., submitted October 31, 2007.

The following grounds of rejection are before us for review:

I. Claims 16 and 17 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Maeda and Nakamoto.

II. Claim 18 stands rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Baldwin '614 and Baldwin '522.

We affirm rejection I, but reverse rejection II.

PRINCIPLES OF LAW

When appealing the Examiner's rejection, Appellants must show error in the Examiner's conclusion of unpatentability. *See Ex parte Yamaguchi*, 88 USPQ2d 1606, 1608 and 1614 (BPAI 2008) (precedential); *Ex parte Fu*, 89 USPQ2d 1115, 1118 and 1123 (BPAI 2008) (precedential); *Ex parte Catan*, 83 USPQ2d 1569, 1570 and 1577 (BPAI 2007) (precedential); *Ex parte Smith*, 83 USPQ2d 1509, 1512-1514, 1519 (BPAI 2007) (precedential).

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Under the correct obviousness analysis, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Thus, for a prima facie case of obviousness to be established, the references need not recognize the problem solved by Appellants. *In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996); *In re Beattie*, 974 F.2d 1309,

1312 (Fed. Cir. 1992). Moreover, in patent prosecution, "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled," which appellants "can then overcome [ ] by proving that the relevant disclosures of the prior art patent are not enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR* 550 U.S. at 418, it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

ISSUE (Rejection I)

The Examiner concludes that claim 16 is rendered obvious by the combination of Maeda and Nakamoto.

Appellants contend that the combination of references relied upon by the Examiner do not establish that lowering uric acid levels would be effective in treating hypertension. Appellants contend further that there was no expectation of success of treating hypertension over the long term with xanthine oxidase inhibitors.

Thus, the issue on appeal is: Have Appellants demonstrated that the Examiner erred in concluding that the prior art relied upon renders the method of claim 16 obvious?

FINDINGS OF FACT

FF1 The Examiner rejects claims 16 and 17 under 35 U.S.C. § 103(a) as being obvious over the combination of Maeda and Nakamoto[2] (Ans. 3). As Appellants do not argue the claims separately, we focus our analysis on claim 16, and claim 17 stands or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF2 The Examiner cites the Maeda patent for its teaching of a treatment for hypertension using a xanthine oxidase inhibitor, such as 4-amino-6-hydroxypyrazolol [3,4-d]pyrimidine (AHPP) (Ans. 4).

FF3 The Examiner further finds that Maeda teaches that the xanthine oxidase inhibitor, AHPP, inhibits uric acid production in a dose dependent manner *in vitro* (*id.*).

FF4 Maeda also demonstrated a drop in blood pressure in spontaneously hypertensive rats (SHR) (Maeda, col. 5-col. 6, Examples 8 and 9).

FF5 Maeda also provides illustrative amounts and methods of administering the xanthine oxidase inhibitor to an adult patient (*id.* at col. 2, l. 58-col. 3, l. 28).

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[2] The Examiner also relies on a purported admission in Appellants' Specification (Ans. 3), but as we do not find it necessary to the obviousness analysis, we will not address the purported admission further.

FF6 The Examiner notes that Maeda does not "explicitly teach the administration of a therapeutically effective amount of xanthine oxidase inhibitor to achieve a uric acid level in the patient of 4 to 6 mg/dl in treating hypertension." (Ans. 4.)

FF7 The Examiner relies on Nakamoto for teaching that allopurinol is known as an agent for lowering uric acid (Ans. 4).

FF8 The Examiner concludes that it would have been obvious to determine the optimal parameters such as the effective amount of xanthine oxidase inhibitor to treat hypertension, and also reduce uric acid levels to the claimed range of 4 to 6 mg/dl as Maeda teaches the use of xanthine oxidase inhibitors to treat hypertension, and also teaches that uric acid production was inhibited by xanthine oxidase inhibitor, AHPP, in a dose dependent manner (*id.* at 4-5).

FF9 The Examiner notes further that xanthine oxidase inhibitors inhibit the conversion of xanthine to uric acid, and as Maeda demonstrates that uric acid production was inhibited by a xanthine oxidase inhibitor, AHPP, in a dose dependent manner, the methods of treating hypertension taught by Maeda would "necessarily result in reducing uric acid levels as recited in the claims, when the amount of AHPP are modified to achieve desired therapeutic effects." (*Id.* at 6.)

FF10 The Declaration Dr. Rodriguez-Iturbe, submitted October 31, 2007, states that "[w]hile I am aware that xanthine oxidase inhibitors have been reported to lower blood pressure transiently" in the SHR rat, and as reported by Maeda, "none of those studies suggested that this was due to uric acid,

but rather asserted that this was due to oxidative stress." (Dr. Rodriguez-Iturbe Declaration, ¶1.)

FF11 The Declaration further states that "[w]hile [xanthine oxidase] inhibitors could have some effects on blood pressure via their antioxidant effects, the observation that they failed to lower BP in longterm [sic] studies in the SHR[ ] taught away those skilled in the art from using them in patients with hypertension." (*Id.* at ¶2.)

FF12 Thus, the Declaration states that "[s]tudies in the SHR rat did not provide a reasonable expectation to those skilled in the art of successfully treating hypertension via administration of [a xanthine oxidase] inhibitor, much less did they teach or suggest to those skilled in the art to use [xanthine oxidase] inhibitors as a means to lower blood pressure by reducing uric acid levels." (*Id.* at ¶3.)

FF13 The Declaration of Dr. George Bakris, dated October 31, 2007, citing the Framingham Heart Study, states that it was longstanding belief "that elevated uric acid in hypertension was a secondary phenomenon and not causative of hypertension." (Dr. George Bakris Declaration, ¶1.)

FF14 Dr. Bakris notes further that the concept that xanthine oxidase inhibitors may be useful in the treatment of hypertension "was thwarted by the fact that these inhibitors did not lower [blood pressure] in longterm [sic] studies in the SHR." (*Id.* at ¶2.)

ANALYSIS

We first note that as we find that Nakamoto was primarily applied to address the limitation of dependent claim 17, and as Appellants do not argue claim 17 separately from claim 16, we will not address that reference further.

Appellants argue as to the Maeda reference that "other than using uric acid as a marker to determine whether the AHPP inhibited xanthine oxidase *in vitro*, nowhere does the Maeda [ ] reference hint that uric acid levels should be targeted as a means to lower blood pressure." (App. Br. 4.) Appellants rely on a Declaration from Dr. Rodriguez-Iturbe, submitted October 31, 2007, which further states that Maeda does not teach that blood pressure was lowered due to the xanthine oxidase inhibitor's affect on uric acid levels, but due to oxidative stress (*id.* at 5). To further press the point that it was unknown that lowering uric acid levels would be effective in treating hypertension, Appellants rely on the Declaration of Dr. George Bakris, submitted October 31, 2007, which also states that it was not known that uric acid levels should be targeted as a means to lower blood pressure (*id.* at 6).

Appellants' arguments are not convincing. First, we note that claim 16 encompasses the use of any xanthine oxidase inhibitor in the treatment of hypertension. Second, the limitation that "a uric acid level in the patient of 4 to 6 mg/dl" is not a positive method step, that is, it does not require a positive step of measuring uric acid levels.

As noted above, the prior art need not recognize the problem solved by Appellants. Thus, it is irrelevant that Maeda did not recognize that uric

acid levels should be targeted in the treatment of hypertension. Maeda does teach the administration of a xanthine oxidase inhibitor to treat hypertension. In addition, we agree with the Examiner that the ordinary artisan would have expected uric acid levels to decrease as Maeda demonstrated that uric acid production was inhibited by the xanthine oxidase inhibitor, AHPP, in a dose dependent manner. Moreover, as also noted by the Examiner, the methods of treating hypertension taught by Maeda would necessarily result in reducing uric acid levels, as recited in the claims, when an amount of xanthine oxidase inhibitor is administered to achieve the desired therapeutic effect, that is, the treatment of hypertension.

Appellants also rely on the Declarations of Dr. Rodriguez-Iturbe and Dr. Bakris to demonstrate that there was no expectation of success of treating hypertension over the long term with xanthine oxidase inhibitors. (App. Br. 5-6.) Specifically, Appellants note that Dr. Rodriguez-Iturbe states that studies in the SHR rat did not provide a reasonable expectation of success of treating hypertension using xanthine oxidase inhibitors, and that Dr. Bakris further states that the inhibitors did not lower blood pressure in long term studies (*id.*). Appellants assert that the Declarations and art establish that, at the time of invention, "no reasonable expectation existed to treat hypertension by controlling uric acid, much less targeting specific uric acid levels." (*Id.* at 11.)

Again, we do not find Appellants' arguments convincing. Maeda, an issued U.S. Patent, is presumed to be enabling for all that it teaches, and Maeda teaches the treatment of hypertension using a xanthine oxidase inhibitor, the same method encompassed by claim 16. While the

Declarations of Dr. Rodriguez-Iturbe and Dr. Bakris state that the use of xanthine oxidase inhibitors did not achieve long term results in the SHR model, the claims do not require long term treatment. Moreover, while the Declarations appear to be arguing that the Maeda reference is not enabling for the treatment of hypertension using a xanthine oxidase inhibitor, other than stating that the xanthine oxidase inhibitor did not have long term efficacy in the SHR model, they do not present any direct evidence demonstrating that the ordinary artisan would have found the teachings of the patent lacking enablement.

CONCLUSION OF LAW

We conclude that Appellants have not demonstrated that the Examiner erred in concluding that the prior art relied upon renders the method of claim 16 obvious.

We thus affirm the rejection of claims 16 under 35 U.S.C. § 103(a) as being obvious over Maeda. As claim 17 stands or falls with claim 16, we affirm the rejection as to that claim as well.

ISSUE (Rejection II)

The Examiner concludes that claim 18 is rendered obvious by the combination of Baldwin '614 and Baldwin '522.

Appellants contend that the Examiner has mischaracterized the teachings of Baldwin '614 and Baldwin '522, and has failed to set forth a prima facie case of obviousness.

Thus, the issue on appeal is: Have Appellants demonstrated that the Examiner failed to set forth a prima facie case of obviousness?

FINDINGS OF FACT

FF15 The Examiner rejects claim 18 under 35 U.S.C. § 103(a) as being obvious over the combination of Baldwin '614 and Baldwin '522 (Ans. 6).

FF16 The Examiner finds that Baldwin '614 teaches "a method of treating hypertension comprising administering [a] xanthine oxidase inhibitor." (*Id.* at 7 (citing Baldwin '614, col. 1, ll. 21-31).)

FF17 Baldwin '614 teaches that it is "known in the art that certain imidazole compounds are useful as xanthine oxidase inhibitors or as anti-hypertensive agents." (Baldwin '614, col. 1, ll. 12-14.)

FF18 Baldwin '614 teaches that "it is an object of the present invention to provide a novel and useful class of compounds which are active as xanthine oxidase inhibitors or in the treatment of hypertension." (*Id.* at col. 1, ll. 21-24.)

FF19 The Examiner notes that Baldwin does not teach the use of the xanthine oxidase inhibitor, allopurinol, for the treatment of hypertension (Ans. 7).

FF20 The Examiner cites Baldwin '522 for teaching that allopurinol is a xanthine oxidase inhibitor (*id.*).

FF21 The Examiner also finds that Baldwin '522 teaches a method of reducing uric acid in a patients by administering trifluoromethylimidazole xanthine oxidase inhibitors, and that the compounds also "exhibit anti-hypertensive activity." (*Id.*)

FF22 Baldwin '522 teaches that allopurinol has been used in the treatment of gout, wherein the allopurinal acts as a specific inhibitor of xanthine oxidase, blocking uric acid synthesis (Baldwin, col. 1, ll. 54-65).

FF23 Baldwin '522 teaches that "[a]n object of this invention is to provide novel 4(5)-trifluoromethylimidazoles which are useful in the treatment of gout and hyperuricemia." (*Id.* at col. 2, ll. 14-16.)

FF24 Baldwin '522 also teaches that "[a] second object of this invention is to describe products which have utility as hypotensive agents and products which are useful in the treatment of bronchoconstriction." (*Id.* at col. 2, ll. 16-19.)

FF25 Baldwin '522 teaches compounds useful in the treatment of gout are:

2-(4-pyridyl)-4(5)-trifluoromethylimidazole
1-methyl-2-(4-pyridyl)4-trifluoromethylimidazole
2-(4-thiazolyl)- 4(5)-trifluoromethylimidazole
2-(2-furyl)-4(5)-trifluoromethylimidazole
1-ethyl-2-(4-thiazolyl)-4-trifluoromethylimidazole
2-isoamyl-4(5)-trifluoromethylimidazole
2-phenyl-4(5)-trifluoromethylimidazole
2-(o-cyanophenyl)-4(5)-trifluoromethylimidazole
2-(p-ethylphenyl)-4(5)-trifluoromethylimidazole
1-propyl-2-phenyl-4-trifluoromethylimidazole
2-vinylphenyl-4(5)-trifluoromethylimidazole
2-(p-sulfamoylphenyl)-4(5)-trifluoromethylimidazole
2-(p-N-methylsulfamoyl)-4(5)-trifluoromethylimidazole
1-methyl-2-(p-sulfamoylphenyl)-4-trifluoromethylimidazole
1-methyl-2 -phenyl-5-trifluoromethylimidazole
2-(p-methoxyphenyl)-4(5)-trifluormethylimidazole
2-(6-quinolyl)-4(5)-trifluoromethylimidazole
2-(3-furyl)-4(5)-trifluoromethylimidazole
2-(2-thienyl)-4(5)-trifluoromethylimidazole
2-(3,4-methylenedioxyphenyl)-4(5)-trifluoromethylimidazole
2-(o-methoxyphenyl)-4(5)-trifluoromethylimidazole

2-(p-acetylaminophenyl)-4(5)-trifluoromethylimidazole
2-(p-cyanophenyl)-4(5)-trifluoromethylimidazole
1-methyl-2-(p-methoxyphenyl)-4-trifluoromethylimidazole
1-methyl-2-(p-methoxyphenyl)-5-trifluoromethylimidazole
2-(p-dimethylaminophenyl)-4(5)-trifluoromethylimidazole
2-(5-indanyl)-4(5)-trifluoromethylimidazole
2-(1-indanyl)-4(5)-trifluoromethylimidazole
2(3,4-dichlorophenyl)-4(5)-trifluoromethylimidazole
2-(m-chlorophenyl)-4(5)-trifluoromethylimidazole
2-(p-fluorophenyl)-4(5)-trifluoromethylimidazole
1-methyl-2-(p-chlorophenyl)-4-trifluoromethylimidazole
2-(p-carboxyphenyl)-4(5)-trifluoromethylimidazole
2-(2-indanyl)-4(5)-trifluoromethylimidazole
2-(2-naphthyl)-4(5)-trifluoromethylimidazole
1-methyl-2-(p-acetylaminophenyl)-4-trifluoromethylimidazole and,
1-(2-hydroxyethyl)-2-(1-naphthyl)-5-trifluoromethylimidazole

(*id.* at col. 4, 27-col. 5, l. 6).

FF26 Baldwin '522 teaches that compounds that exhibit anti-hypertensive activity are:

2-(3-pyridyl)-4(5)-trifluoromethylimidazole
2-(2-pyridyl)-4(5)-trifluoromethylimidazole
2-(4-pyridyl)-4(5)-trifluoromethylimidazole
2-(4-thiazolyl)-4(5)-trifluoromethylimidazole
2-isopropyl-4(5)-trifluoromethylimidazole
2-(2-thienyl)-4(5)-trifluoromethylimidazole
2-(o-chloropheny)-4(5)-trifluoromethylimidazole
2-(p-chlorophenyl)-4(5)-trifluoromethylimidazole
2-phenyl-4(5)-trifluoromethylimidazole
2-(p-methylsulfonamidophenyl)-4-trifluoromethylimidazole
2-(p-diethylaminoethoxyphenyl)-4-trifluoromethylimidazole
2-(3-pyridyl-1-oxide)-4-trifluoromethylimidazole
2-diphenylmethyl-4-trifluoromethylimidazole
2-(1-methyl-4-pyrazolyl)-4-trifluoromethylimidazole
2-(2-methyl-4-pyridyl)-4-trifluoromethylimidazole
2-(6-methyl-3-pyridyl)-4-trifluoromethylimidazole

2-(6-quinolyl)-4(5)-trifluoromethylimidazole
1-methyl-2-phenyl-4-trifluoromethylimidazole, and
1-methyl-2-(p-chlorophenyl)-5-trifluoromethylimidazole

(*id.* at col. 6, ll. 28-52).

FF27 Thus while certain compounds, such as 2-(4-pyridyl)-4(5)-trifluoromethylimidazole, may appear on both lists, the differences in the two lists demonstrate that Baldwin '522 does not generically teach that compounds that are useful in the treatment of gout also have anti-hypertensive activity.

FF28 The Examiner concludes that it would have been obvious to the ordinary artisan at the time of invention to use allopurinol to treat hypertension "because 1) Baldwin '614 teaches that xanthine oxidase inhibitors are useful in treating hypertension, and 2) Baldwin [ ] '522 teach[es] that allopurinol acts as a specific inhibitor of the enzyme xanthine oxidase." (Ans. 7.)

ANALYSIS

Appellants argue that Baldwin teaches "a new class of substituted imidazole compounds," and "stresses that certain compounds of the class are useful as either an anti-hypertensive agent or as a xanthine oxidase inhibitor." (App. Br. 11.) Thus, Appellants argue, Baldwin does not "connect the inhibition of xanthine oxidase with the lowering of blood pressure, and in fact suggests that the inhibition of xanthine oxidase and the lowering of blood pressure involve[ ] different imidazole compounds." (*Id.*) Thus, Appellants assert that "it is unfair to make the logical leap that just because certain imidazole derivatives can be used as anti-hypertensive

agents, that allopurinol, an entirely different class of compound that happens to be a xanthine oxidase inhibitor, can be used to treat hypertension." (*Id.* at 11-12.)

We agree with Appellants. Baldwin '614 provides "a novel and useful class of compounds which are active as xanthine oxidase inhibitors or in the treatment of hypertension" (FF18), thus suggesting that the agents are one or the other, but not necessarily both. That interpretation is reinforced by Baldwin '522, in which one object of the invention is to provide novel compounds that are useful in the treatment of gout, whereas a second objective is to provide novel compounds that demonstrate anti-hypertensive activity. The two lists of compounds provided by Baldwin '522 that have those two different activities are not identical, further demonstrating that the two Baldwin references do not teach that just because a compound is a xanthine oxidase inhibitor, it would also be expected to have anti-hypertensive activity. Therefore the ordinary artisan would not conclude from the teachings of Baldwin '614 and Baldwin '522 that every xanthine oxidase inhibitor, such as allopurinol, would also be useful in the treatment of hypertension.

CONCLUSION OF LAW

We conclude that Appellants have demonstrated that the Examiner failed to set forth a prima facie case of obviousness.

We are thus compelled to reverse the rejection of claim 18 under 35 U.S.C. § 103(a) as being obvious over the combination of Baldwin '614 and Baldwin '522.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED-IN-PART

cdc

MCDERMOTT, WILL & EMERY
600 13TH STREET, N.W.
WASHINGTON DC 20005-3096